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— *of inventorship (Rule 4.17(iv))*

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(54) Title: EXTENDED RELEASE FORMULATION OF PRAMIPEXOLE DIHYDROCHLORIDE

(57) Abstract: An extended release composition of Pramipexole or a pharmaceutical acceptable salt thereof, wherein the active agent is coated on a non pareil inert core, the drug loaded core is further coated with a polymeric layer which enables the release of the active agent over an extended period and optionally the extended release pellets being further blended with suitable excipients and compressed into a multi unit tablet and processes for the preparation of the said composition.

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Extended Release Formulation of Pramipexole Dihydrochloride

The present invention relates to the process of preparing extended release formulation of Pramipexole. The formulation of the present invention is an extended release pellets. Pramipexole is a dopamine D2 receptor agonist useful in treatment of Parkinson's disease. Pramipexole as its dihydrochloride salt is commercially available as MIRAPEX tablets of Pharmacia & Upjohn. These are immediate-release tablets in 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg and 1.5 mg strengths, designed for oral administration of a single tablet three times per day to provide a daily dose of 0.375 to 4.5 mg. Doses herein are expressed in amounts of pramipexole dihydrochloride monohydrate unless otherwise specified; 1.0 mg pramipexole dihydrochloride monohydrate is equivalent to about 0.7 mg pramipexole base.

The chemical name of pramipexole dihydrochloride is (*S*)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate (Fig. 1). Its empirical formula is C10H17N3S • 2 HCl • H2O, and its molecular weight is 302.27. Pramipexole dihydrochloride is a white to off-white powder substance. Pramipexole dihydrochloride is more than 20% soluble in water, about 8% in methanol, about 0.5% in ethanol, and practically insoluble in dichloromethane.

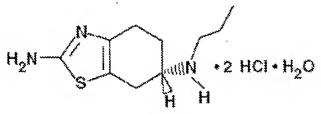

Fig. 1: Structure of Pramipexole dihydrochloride.

The primary indication for the drug, Parkinson's disease, is an affliction that becomes more prevalent with advancing age and is often accompanied by decline in memory (elderly patients). Though a three times daily dosing regimen for immediate-release pramipexole dihydrochloride tablets is well tolerated, for

enhancing patient compliance a once-daily regimen is explored in International patent applications, WO 2004010999, WO 2004010997 A1 and WO 04010982.

The process covered under these patent applications involve the preparation of hydrophilic matrix tablet using hydroxypropyl methylcellulose (HPMC) as the rate controlling polymer and pregelatinized starch of a specific tensile strength as the filler. The tablet is prepared by the process of direct compression wherein all the ingredients except lubricant are blended first in a V-blender for 10 to 30 minutes at 24 rpm, lubricant is added to it and mixed for few minutes and finally the blend is compressed into tablet. The hydrophilic matrix tablet is further coated with a rate controlling ethyl cellulose (EC). The rate is also controlled by the formation of pores due to hydroxypropyl methylcellulose inside the diffusion layer of ethyl cellulose.

The prior art mentions that side-effect profile will be less with once daily dosage form compared to thrice daily immediate release dosage form. It identifies an in vitro release profile that would be characteristic of a well tolerated once-daily dosage form of pramipexole. It also provides an in-vivo pharmacokinetic (PK) profile that would be consistent with good therapeutic efficacy while not causing an unacceptable incidence or severity of side effects.

There are limitations of the prior art. These are

1. It involves a synergistic approach among HPMC and EC in obtaining extension of drug release. Therefore, for all the five strengths, a different composition is required to be derived for having the same dissolution profile. It does not show any possibility for having a step-up step-down composition. There is no correlation among the composition for all the strength. Although the composition is same qualitatively but is different quantivatitively. The percentage of ingredients in the final dosage form varies for all the five strengths.

2. Very low level of coating (3 to 5 %) of the rate controlling polymer of the dosage form. So there is high possibility of having variation in the coating thickness, specifically at the edges of the tablet.
3. Extremely lower dose of 375 and 750 micrograms can pose a problem of content non-uniformity during compression of the tablets.

The dosage form in international patent application WO2004010999 provides an extended release product with the following probable *in vitro* dissolution specifications:

Time (h)	1 % dissolved	2 % dissolved	3 % dissolved
0	0	0	0
1	15	11	0
2	24	20	0.5
4	36	34	15
6	47	46	23
8	55	55	29.6
12	69	70	41.6
16	79	80	51.1
24	90	92	64.8

Protocol: USP apparatus I, 900 ml 0.05M Phosphate Buffer pH 6.8, 100 rpm, 37°C.

In the present invention an alternative once daily extended release formulation is developed. It describes a process which overcomes the limitation of prior invention. The process of the earlier invention necessitates the development of a unique formula for all strengths, whereas present invention discloses step-up step-down composition, which adds to a very high degree of convenience to the fabricator of the product.

United state patent application No. 20050118264 discloses an extended release composition comprising as active compound Venlafaxine Hydrochloride, in which Venlafaxine Hydrochloride is coated on a non pareil inert core, which coated core is then coated with polymeric layer which enables the controlled release of the Venlafaxine Hydrochloride. The present invention comprises of pramipexole dihydrochloride, as active compound. Pramipexole dihydrochloride is low dose, highly photosensitive and characteristically different active than the venlafaxine hydrochloride. The process in the present invention provides uniform content and dose loading.

The present invention of extended release formulation comprising of pramipexole dihydrochloride and pharmaceutically acceptable excipients. Pramipexole dihydrochloride is coated on a non pareil inert core, said coated core is then coated with a polymeric layer which enables the controlled release of pramipexole dihydrochloride. Pramipexole dihydrochloride comprises 0.01 to 10.0 % w/w of the coated pellets.

In a preferred embodiment of the present invention, pramipexole dihydrochloride is suitably admixed with binder, said binder is selected from polyvinyl pyrrolidone (povidone), hydroxypropyl cellulose, hydroxypropyl methylcellulose, etc. Binder preferably comprises 0.5 to 20 % w/w of the coated pellets. The non-pareil inert core can be either inert sugar core or microcrystalline cellulose core or the equivalents thereof. The composition preferably comprises 10 to 90 % of the core per weight of the coated pellets. Advantageously the coated core is then coated with an isolating layer (sub coating). Isolating (sub-coating) layer composed of polymers selected from polyvinyl pyrrolidone, hydroxypropyl methylcellulose, microcrystalline cellulose, Hydroxypropyl cellulose, carrageenan, glyceryl monostearate, etc. The sub coating layer comprises of 0.5 to 10 % w/w of the coated pellets.

The sub-coating layer is then coated with an additional polymeric layer which enables the extended release of pramipexole dihydrochloride. Said additional polymeric layer composed of hydrophobic polymer, hydrophobic or hydrophilic plasticizer and /or hydrophilic pore forming polymer. Said additional polymeric layer is suitably sprayed over the coated non-pareil layer or over the sub-coating layer. The hydrophobic polymer used in said additional polymeric layer are polyvinyl acetate, eudragit, cellulose derivatives such as ethyl cellulose, cellulose acetate, etc. The hydrophilic pore forming polymers in said additional polymeric layer are copolyvidone, polyvinyl pyrrolidone, polyethylene glycols, hydroxylpropyl methyl cellulose, hydroxyethyl cellulose, etc. The plasticizer in said additional polymeric layer are dibutyl sebacate, triethyl citrate, castor oil, glyceryl monostearate, diethyl phthalate, glyceryl trihepthanoate, etc. The additional polymeric coating layer may also be wax based coating. The composition preferably comprises 2.0 to 60.0% of hydrophobic polymer per weight of the coated pellets; Nil to 25 % per weight of hydrophillic pore forming polymer of the coated pellets and preferably Nil to 10 % of plasticizer per weight of the coated pellets.

The above process is a conventional process and can be performed in fluidized bed coating system with preference to bottom spray mechanism. The pellets obtained are either suitably filled into hard gelatin capsules or compressed into tablets. The tablet if dispersible, will have suitable flavor. The tablet for swallowing may be coated with a non functional film coating; process is common to the person with limited skills in the art. When the small coated particles of pramipexole dihydrochloride are tabletted they are mixed with additives e.g. microcrystalline cellulose such as Avicel PH 102, Avicel PH 301, Avicel.RTM., which improves the tabletting properties and facilitates the disintegration of the tablet, whereby the individual beads are liberated .

The present invention can be illustrated by the following examples without being limited by them.

Example 1 to 6

Pramipexole Dihydrochloride sustained release pellets were prepared having the composition shown in Table 1.

Drug Layering: Hydroxypropyl Methylcellulose (3cps) was dispersed in purified water and pramipexole dihydrochloride was disolved in the formed dispersion. This dispersion was coated on sugar spheres (700 micron) using a fluid bed coater.

Sub coating: Sub coating solution was prepared by dissolving povidoneK-30 in denatured ethanol. This solution was coated on drug loaded pellets using a fluid bed coater.

Functional coating: Functional coating solution was prepared by dispersing ethocel 45 cps in denatured ethanol. The polymer was allowed to hydrate for 10 hrs and form a clear dispersion. Dibutyl sebacate was added to the solution just 1 hour before coating and mixed well. Solution was coated on sub coated pellets using a fluid bed coater.

Table 1: Composition of pramipexole dihydrochloride pellets of example 1 to 6.

Ingradient	Quantity (mg)					
	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
Drug layering stage						
Pramipexole dihydrochloride	0.375	0.375	0.375	0.375	0.375	0.375
HPMC 3cps	37.5	37.5	37.5	37.5	37.5	37.5
Purified water	qs	qs	qs	qs	qs	qs
Sugar spheres	150	150	150	150	150	150
Sub coating stage						
Povidone K 30	3.76	3.76	3.76	3.76	3.76	3.76
Ethanol	37.58	37.58	37.58	37.58	37.58	37.58
Functional coating stage						
Ethyl cellulose 45cps	8.52	13.63	17.03	20.44	23.85	30.66
Ethanol	319.4	511.04	638.8	766.56	894.32	1149.84
Dibutyl sebacate	0.95	1.52	1.89	2.27	2.65	3.41
Total	**201.11**	**206.79**	**210.56**	**214.35**	**218.14**	**225.71**

Example 7:

Dissolution profiles of the pramipexole dihydrochloride pellets of each of Examples 1 to 6 were evaluated under the following conditions. USP apparatus 1 was used to stir a dissolution medium (900 ml of phosphate buffer at a pH of 6.8) at a spindle rotation speed of 100 rpm and a temperature of 37°C. The dissolution rate was shown in Table 2.

Table 2: In vitro dissolution data for example 1 to 6.

Time (hr)	% dissolved					
	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
0	0	0	0	0	0	0
1	31	14	13	11	9	5
2	53	30	26	23	19	14
4	72	53	49	44	39	31
6	83	66	62	57	51	44
8	89	73	70	66	60	53
12	93	81	-	-	70	-
24	-	-	-	87	84	80

Example 8

Multi-particulate tablets of Pramipexole dihydrochloride sustained release pellets were prepared having the composition shown in Table 3.

All ingredients except pramipexole dihydrochloride pellets and lubricants were screened to remove lumps and blended thoroughly for 30 minutes with Pramipexole dihydrochloride pellets using conta blender at 15 rpm. The screened lubricant was then blended with it for further 3-5 min. The resulting mixture was compressed.

Table 3: Composition of pramipexole dihydrochloride multi-particulate tablets of Example 8

Ingredients	Quantity (mg)
Pramipexole dihydrochloride pellets (Example 6)	225.71
Talc	0.75
Micro crystalline cellulose PH 301	486.85
Micro crystalline cellulose PH 102	243.69
Cross carmellose sodium	18.00
Aerosil 200	1.5
Sodium stearyl fumerate	1.5
Total	**978.0**

Example 9

Pramipexole Dihydrochloride sustained release pellets were prepared having the composition shown in Table 4.

Drug Layering: Hydroxypropyl Methylcellulose (3cps) was dispersed in purified water and pramipexole dihydrochloride was disolved in the formed dispersion. This dispersion was coated on microcrystalline cellulose beads (500 – 710 micron) using a fluid bed coater.

Functional coating: Functional coating solution was prepared by dispersing Surelease E7 19010 in purified water. The polymer was allowed to mix for 60 minutes and form a uniform dispersion. Solution was coated on sub coated pellets using a fluid bed coater.

Example 10

Pramipexole Dihydrochloride sustained release pellets were prepared having the composition shown in Table 4.

Drug Layering: Povidone K30 was dispersed in purified water and pramipexole dihydrochloride was disolved in the formed dispersion. This dispersion was coated on microcrystalline cellulose beads (500 – 710 micron) using a fluid bed coater.

Sub coating: Sub coating solution was prepared by dissolving povidone K30 in purified water. This solution was coated on drug loaded pellets using a fluid bed coater.

Functional coating: Functional coating solution was prepared by dispersing Surelease E7 19010 in purified water. The polymer was allowed to mix for 60 minutes and form a uniform dispersion. Solution was coated on sub coated pellets using a fluid bed coater.

Table 4: Composition of pramipexole dihydrochloride pellets of example 9 - 11.

Ingradient	Quantity (mg)		
	Example 9	Example 10	Example 11
Drug layering stage			
Pramipexole dihydrochloride	3.0	3.0	3.0
HPMC 3cps	3.0		21.0
Povidone K 30		6.0	
Purified water	qs	qs	qs
Celphere CP 203	-	-	263
Celphere CP 507	281	275	-
Sub coating stage			
HPMC 3cps	-	-	8.0
Povidone K 30	-	3.0	-
Purified water	-	qs	qs
Functional coating stage			
Surelease E7 19010	25.83	23.0	-
Ethocel 45 cps	-	-	17.7
HPMC 3cps	-	-	4.42
Purified water	qs	qs	-
Denatured ethanol	-	-	qs
Total	**312.83**	**310.0**	**317.12**

Example 11

Pramipexole Dihydrochloride sustained release pellets were prepared having the composition shown in Table 4.

Drug Layering: Hydroxypropyl Methylcellulose (3cps) was dispersed in purified water and pramipexole dihydrochloride was disolved in the formed dispersion. This dispersion was coated on microcrystalline cellulose beads (150 - 300 micron) using a fluid bed coater.

Sub coating: Sub coating solution was prepared by dissolving Hydroxypropyl Methylcellulose (3cps) in purified water. This solution was coated on drug loaded pellets using a fluid bed coater.

Functional coating: Functional coating solution was prepared by dispersing ethocel 45 cps in denatured ethanol. The polymer was allowed to hydrate for 10 hrs and form a clear dispersion. Hydroxypropyl Methylcellulose (3cps) was added to the solution and allowed to hydrate to form the clear solution. Solution was coated on sub coated pellets using a fluid bed coater.

Example 12

Pramipexole Dihydrochloride sustained release pellets were prepared having the composition shown in Table 5.

Drug Layering: Povidone K30 was dispersed in purified water and pramipexole dihydrochloride was disolved in the formed dispersion. This dispersion was coated on microcrystalline cellulose beads (500 – 710 micron) using a fluid bed coater.

Sub coating: Sub coating solution was prepared by dissolving Povidone K30 in purified water. This solution was coated on drug loaded pellets using a fluid bed coater.

Functional coating: Functional coating solution was prepared by dispersing ethocel 7 cps in denatured ethanol. The polymer was allowed to hydrate for 10 hrs and form a clear dispersion. Povidone K30 was added to the solution and allowed to hydrate to form the clear solution. Solution was coated on sub coated pellets using a fluid bed coater.

Table 5: Composition of pramipexole dihydrochloride pellets of example 12.

Ingradient	Quantity (mg)
Drug layering stage	
Pramipexole dihydrochloride	3.0
Povidone K 30	24
Purified water	qs
Celphere CP 507	275
Sub coating stage	
Povidone K 30	9
Purified water	Qs
Functional coating stage	
Ethocel 7 cps	28
Povidone K30	3.11
Denatured ethanol	Qs
Total	**342.1**

Example 13:

Dissolution profiles of the pramipexole dihydrochloride pellets of each of Examples 8 to 12 were evaluated under the following conditions. USP apparatus 1 was used to stir a dissolution medium (900 ml of phosphate buffer at a pH of 6.8) at a spindle rotation speed of 100 rpm and a temperature of 37°C. The dissolution rate was shown in Table 6.

Table 6: In vitro dissolution data for example 8 to 12.

Time (hr)	% dissolved				
	Example 8	Example 9	Example 10	Example 11	Example 12
0	0	0	0	0	0
1	22	6	12	16	18
2	34	11	21	28	32
4	50	24	37	41	50
6	61	39	48	48	62
8	69	53	56	54	68
12	78	73	67	61	77
16	84	83	74	66	82
24	91	91	83	71	87

CLAIMS

1. An extended release composition of Pramipexole or a pharmaceutical acceptable salt thereof, in which active agent is coated on a non pareil inert core, the drug loaded core is further coated with a polymeric layer which enables the release of the active agent over an extended period and optionally the extended release pellets are further blended with suitable excipients and compressed into a multi unit tablet.

2. A composition according to Claim 1, where in said salt is Pramipexole dihydrochloride.

3. A composition according to Claim 1, wherein the composition comprises 0.01 – 10 % of Pramipexole dihydrochloride per weight of the total dosage form.

4. A composition according to Claim 1, wherein the composition comprises about 0.125 to about 6 mg pramipexole, expressed as pramipexole dihydrochloride monohydrate equivalent, per dosage unit.

5. An extended release formulation of Pramipexole or a pharmaceutical acceptable salt thereof, having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in Phosphate Buffer pH 6.8 at 37 degree. C:

Time (hours)	Average % Pramipexole released
1	<25
6	30-60
12	55-75
24	>80

6. A composition according to Claim 1, wherein the Pramipexole dihydrochloride is suitably admixed with binder.

7. A composition according to Claim 6, wherein the composition comprises 0.5%-20% of the binder per weight of the total dosage form.

8. A composition according to Claim 7, wherein the binder is selected among polyvinyl pyrrolidone (povidone), hydroxypropyl cellulose and Hydroxypropyl methylcellulose.

9. A composition according to Claim 1, which comprises 10 - 90% of the non pareil core per weight of the total dosage form.

10. A composition according to Claim 9, wherein the non pareil inert core can be either inert sugar core, silicon dioxide or microcrystalline cellulose core or the equivalents thereof.

11. Preparation according to claim 10, wherein the non pareil inert cores have a size of 0.1-1.0 mm.

12. A composition according to Claim 1, wherein the core and/or the core coated with pramipexole dihydrochloride is coated with an isolating/protecting layer composed of polymers selected from polyvinyl pyrrolidone, hydroxypropyl methylcellulose, microcrystalline cellulose, Hydroxypropyl cellulose, carrageenan and glyceryl monostearate.

13. A composition according to Claim 12, wherein the isolating layer is comprised of 0.5-10% of the isolating layer per weight of the total dosage form.

14. A composition according to Claim 1, wherein the extended release polymeric layer is composed, e. g. of a hydrophobic polymer, hydrophobic or hydrophilic plasticizer and /or hydrophilic release modulator polymer.

15. A composition according to Claim 1, which comprises 2 - 60% of the hydrophobic polymer per weight of the total dosage form, optionally up to 25 % of the hydrophillic release modulator polymer per weight of the total dosage form and/or optionally upto 20 % of the plasticizer per weight of the total dosage form.

16. A composition according to Claim 15, wherein said hydrophobic coating polymers are selected among polyvinyl acetate, eudragit, cellulose derivatives such as ethyl cellulose, cellulose acetate and their plasticizers are selected among dibutyl sebacate, triethyl citrate, castor oil, glyceryl monostearate, diethyl phthalate, glyceryl trihepthanoate.

17. A composition according to Claim 15, wherein the hydrophilic release modulator polymer is selected among copolyvidone, polyvinyl pyrrolidone, polyethylene glycols, hydroxylpropyl methyl cellulose and hydroxyethyl cellulose.

18. A pharmaceutical preparation containing the controlled release preparation according to claim 1 filled into hard gelatin capsules.

19. A pharmaceutical preparation comprising the controlled release preparation according to claim 1 and pharmaceutical additives compressed to tablets which disintegrate to release the preparation when the tablets are brought into contact with gastro-intestinal fluids.

20. A method for preparing the composition according to Claim 1, comprising the steps of:

I. dissolving Pramipexole dihydrochloride and binder in a suitable solvent system to prepare a clear solution;
II. applying coat to non pareil inert core with above solution using fluid bed processor;
III. the drug loaded core is further coated with isolating/protecting coat.
IV. the above core is further coated with a polymeric layer which enables the release of the active agent over an extended period;
V. filling of extended release pellets into hard gelatin capsules;
VI. optionally blending the pallets with suitable excipients and compressing into a multi unit tablet.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
A61K9/52 A61K9/26 A61K31/428

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/010982 A (PHARMACIA CORPORATION; LEE, ERNEST, J; HEIMLICH, JOHN, M; NOACK, ROBER) 5 February 2004 (2004-02-05) cited in the application	1-17
Y	paragraph [0002] paragraph [0014] - paragraph [0019] examples 1-7 figure 1 claims 1,6-11,13-15	18-20
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2006	05/04/2006

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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of documents, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/010999 A (PHARMACIA CORPORATION; LEE, ERNEST, J; BREDAEL, GERARD, M; BALDWIN, JO) 5 February 2004 (2004-02-05) cited in the application paragraph [0001] - paragraph [0005] paragraph [0014] paragraph [0018] paragraph [0046] - paragraph [0051] paragraph [0082] - paragraph [0086] examples 1-6 figure 1 table 7 claims 1-4,7,11-18	5
Y	WO 2004/087175 A (PHARMACIA CORPORATION; NOACK, ROBERT, M; HEIMLICH, JOHN, M; LEE, ERNES) 14 October 2004 (2004-10-14) paragraph [0002] paragraph [0012] - paragraph [0013] paragraph [0024] paragraph [0034] paragraph [0036] - paragraph [0039] page 6, line 6 - line 8 claims 1-3,5,6,8-10,12	18-20
A	WO 03/053402 A (PHARMACIA CORPORATION; HEIMLICH, JOHN, M; NOACK, ROBERT, M; COX, STEVE) 3 July 2003 (2003-07-03) page 1, line 10 - line 12 page 4, line 27 - page 5, line 10 page 7, line 24 - line 27 page 15, line 3 - line 17 page 16, line 16 - page 17, line 25 claims 1,2,4,5,17-22,25-27,29-36	1-20
E	WO 2006/015943 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 16 February 2006 (2006-02-16) page 1, line 5 - line 9 page 4, line 27 - page 5, line 2 page 5, line 22 - line 29 page 6, line 7 - line 20 page 9, line 20 - line 29 figures 1-3 examples 1-8 claims 1,3,5-12,14-19,21-24	1-11, 14-19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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